



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,055	04/21/2005	Inger Mattsby-Baltzer	SYNE S2400.1	4089
24184	7590	03/12/2008	EXAMINER	
LYNN E BARBER			GANGLE, BRIAN J	
P O BOX 16528			ART UNIT	
FORT WORTH, TX 76162			PAPER NUMBER	
			1645	
			MAIL DATE	
			DELIVERY MODE	
			03/12/2008	
			PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/532,055	Applicant(s) MATTSBY-BALTZER ET AL.	
	Examiner BRIAN J. GANGLE	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 January 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21-24, 27-29 and 34-36 is/are pending in the application.
- 4a) Of the above claim(s) 21-23, 27, 29 and 34-36 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 24, 28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/14/2008 has been entered.

The amendment and remarks, filed 1/14/2008, are acknowledged. Claims 24 and 28 are amended. Claim 25 is cancelled. Claims 21-24, 27-29, and 34-36 are pending. Claims 21-23, 27, 29, and 34-36 are withdrawn as being drawn to non-elected inventions. Claims 24 and 28 are currently under examination.

It is noted that applicant has listed incorrect status identifiers for claims 26, 30-33, and 37-39. These claims were cancelled in the amendment filed on 4/11/2007. In the next amendment, applicant should use the correct status identifiers. In addition, the text of the claim should not be included for cancelled claims.

Objections Withdrawn

The objection to the specification for the use of the trademarks is withdrawn in light of applicant's amendment thereto.

New Objections

The disclosure is objected to because of the following informalities: in the system of binomial nomenclature used by scientists, an organism is referred to by its genus name and its species name. The first recitation of an organism's name should include the full recitation of the genus name, which can thereafter be abbreviated using the first letter. However, this can be done only when the meaning is completely unambiguous and no other genus name beginning with the same letter is used in intervening text. The instant specification has numerous references to organisms such as *C. albicans* and *C. neoformans*, which are from different genera. When

Art Unit: 1645

multiple genera that begin with the same letter are referenced, the full name should be spelled out.

Appropriate correction is required.

Claims 24 and 28 are objected to because of the following informalities: genus and species names should be italicized

Appropriate correction is required.

Claim Rejections Withdrawn

The rejection of claims 24-25 and 28 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the phrase, “reactive with a β (1-3)- and/or a β (1-3) (1-6)-glucan epitope in free form, in cell wall fragments or on an intact cell surface and available in cell wall fragments of *C. albicans* and/or *C. neoformans*, or on the cell surface of *C. albicans*, *C. parapsilosis*, *C. krusei*, *C. glabrata* and/or *C. neoformans*,” is withdrawn in light of applicant's amendment and arguments.

The rejection of claim 25 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn, as the cancellation of the claim renders the rejection moot.

The rejection of claims 24 and 28 under 35 U.S.C. 102(b), as being anticipated by Wakshull *et al.* (PCT Publication WO 99/31510, 6/1999), is withdrawn in light of applicant's amendment thereto.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Art Unit: 1645

The rejection of claims 24 and 28, under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained for the reasons set forth in the previous office action.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues:

1. That while the examiner has argued that one would be unable to differentiate between plant species and particular fungal species, the claimed invention is for diagnosis of a Candida fungal infection in a human patient. Applicant argues that a positive result of the invention is that analyzing a mucosal or urine sample allows one to know that there is a fungal infection, and that such an infection is likely a Candida infection because “it is well-known that if there is a fungal infection of a human, this infection is likely to be Candida.” Applicant also asserts that plant infections are not typically a human problem, so one would not find a plant infection upon analysis.

2. That it is clear, from the disclosure, that use of a monoclonal antibody reactive with a Candida $\beta(1-3)$ glucan - and/or a $\beta(1-3)(1-6)$ glucan - epitope in free form, in cell wall fragments, or on an intact cell surface and available in cell wall fragments would be useful in detecting fungal infections, in particular, Candida infections. Applicant asserts that it is well known in the art how to prepare antibodies for such antigens. Applicant also asserts that what is unique about their invention is the diagnosis of a fungal infection in a human patient by assaying mucosal secretions or urine of the patient. Applicant argues that, because of this, one does not need to know what epitope is allowing the diagnosis, but just how to carry out the methods known in the art to accomplish the results of the invention.

3. That, while the examiner cited the Noelle case, where there was insufficient support for claims to a particular antibody, the instant claims are not claims to antibodies, but are claims drawn to methods for diagnosis. Therefore, applicant argues, the examiner's statement that applicant has not characterized the antigen to which the claimed antibody binds is not relevant. Applicant also argues that it is well known in the art how to obtain antibodies to the antigens, as

Art Unit: 1645

discussed in the specification and that "one does not need to know the specifics about an antibody if one has an antibody with certain characteristics and uses it according to the claimed, and well-characterized invention."

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, the claims are not drawn to methods of detecting fungal infections that are "likely" caused by *Candida*. The claims are drawn to methods of diagnosing *Candida* vaginitis or mucocutane candidiasis using antibodies that bind to *Candida* glucans. This requires antibodies that do not bind to glucans from other organisms and requires that one be able to differentiate between fungal species as well as between *Candida* that is present as normal flora and *Candida* that is causing a particular disease. Moreover, the fact that an infection is "likely" caused by *Candida* in no way means that it *is* caused by *Candida*. There are other fungal pathogens that cause disease in humans. In particular, *Aspergillus* and *Cryptococcus* both contain glucans that are identical to those found in *Candida* and both are human pathogens. In fact, it is noted that the instant claims specifically encompass antibodies that bind to *Cryptococcus neoformans*. The examiner sees no way that one could use an antibody that binds to multiple species of fungi to differentiate between those species. More importantly, neither the specification nor the art provides any way for this to occur. In addition, while one would not expect a human to be infected by a plant, humans often consume plants, thus providing a way that mucosal secretions could contain β -glucans from plants.

Regarding argument 2, applicant's arguments are not commensurate in scope with the claims. As stated above, the claims are not limited to methods of detecting fungal infections. They are limited to methods of diagnosing *Candida* vaginitis or mucocutane candidiasis. While those of skill in the art are quite capable of preparing antibodies that would allow detection of β -glucans, there is no means provided, in either the art or the specification, that would allow one of skill in the art to prepare antibodies to *Candida* $\beta(1-3)$ - and/or a $\beta(1-3)$ (1-6)-glucan epitope in free form, or available in cell wall fragments of *C. albicans* and/or *C. neoformans*, or on the cell surface of *C. albicans*, *C. parapsilosis*, *C. krusei*, *C. glabrata* and/or *C. neoformans* that would allow one to diagnose *Candida* vaginitis or mucocutane candidiasis. Even so, when arguing that one could obtain the required antibodies using the methods shown in the specification, applicant is arguing that the invention is enabled. Enablement requires that the specification show how to

Art Unit: 1645

make the invention. Written description requires that applicant convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. Describing a method for obtaining the invention does not demonstrate that applicant was in possession of the invention. With regard to applicant's assertion that one does not need to know what epitope is allowing the diagnosis, in order for the claimed method to be described, the antibodies necessary for said method must be described. This can be accomplished in two ways. The antibodies themselves can be described, or the epitope to which they bind can be described. In the instant case, the epitope has been described only generally as being from a $\beta(1-3)$ glucan - and/or a $\beta(1-3)(1-6)$ glucan. Since these molecules are found in numerous species, this is insufficient to describe the antibodies necessary to practice the invention. The antibodies are described only by the designations A10A. This designation provides no structural information whatsoever, and in addition, this antibodies does not allow diagnosis of *Candida* vaginitis or mucocutane candidiasis.

Applicant's statement that the unique feature of the invention is assaying mucosal secretions or urine is not relevant to whether the method has been described sufficiently. However, it is noted that methods of detecting $\beta(1-3)$ -glucans, $\beta(1-3)(1-6)$ -glucan, and fungal infections by assaying mucosal secretions or urine have already been disclosed in the art. These are not currently being cited in a rejection under 35 U.S.C. 102 because one cannot diagnose *Candida* vaginitis or mucocutane candidiasis simply by detecting the presence of $\beta(1-3)$ -glucans and/or $\beta(1-3)(1-6)$ -glucans.

Regarding argument 3, as evidenced by the restriction requirement mailed on 2/21/2006, the examiner is well aware that the claims are drawn to methods and not to antibodies. However, it is noted that one of the claimed method steps is "assaying mucosal secretions or urine of the patient with at least one antibody." Therefore, to practice the method, one must actually have the antibody and in order for the method to meet the written description requirements, there must be sufficient description of the antibodies.

As outlined previously, the instant claims are drawn to methods of diagnosis of a fungal infection (*Candida* vaginitis or mucocutane candidiasis), comprising assaying with at least one antibody that is reactive with a *Candida* $\beta(1-3)$ -glucan and/or a $\beta(1-3)(1-6)$ -glucan epitope in

Art Unit: 1645

free form or available in cell wall fragments of *C. albicans* and/or *C. neoformans*, or on the cell surface of *C. albicans*, *C. parapsilosis*, *C. krusei*, *C. glabrata* and/or *C. neoformans*.

The courts have recently decided in *Randolph J. Noelle v Seth Lederman, Leonard Chess and Michael J. Yellin* (CAFC, 02-1187, 1/20/2004) that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568. Therefore, based on our past precedent, as long as an applicant has disclosed a "fully characterized antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen. Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites *Enzo Biochem II* for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application.

In the instant application, applicant has failed to "fully characterize" the antigen (i.e. $\beta(1,3)$ - and/or $\beta(1,3)(1,6)$ -glucan epitopes) to which the claimed antibody binds. The instant claims are drawn to all monoclonal antibodies with specificity to any $\beta(1,3)$ - and/or $\beta(1,3)(1,6)$ -glucan epitope. If one were to limit the epitope to $\beta(1,3)$ - and/or $\beta(1,3)(1,6)$ -glucans, these

Art Unit: 1645

polysaccharides are found in numerous plants and species of fungi, thus one would be unable to differentiate between plant species and particular fungal species. The specification is silent regarding what epitopes would allow one to differentiate between species.

The specification refers to the antibody "A10A," which refers to a laboratory designation for a monoclonal antibody. Said designation does not provide any structural or functional limitations. Moreover, there is no description in the application of the structure of said antibody. Consequently, since applicant has not fully characterized the antigen to which the claimed antibodies bind, the written description requirements under 35 U.S.C. 112, first paragraph have not been met.

The specification does not describe, with any degree of specificity, the $\beta(1,3)$ - and/or $\beta(1,3)(1,6)$ -glucan associated epitopes to which the members of the claimed genus of antibodies must bind in order to achieve the desired immunological response, such that the specification might reasonably convey to the skilled artisan that applicant had possession of the claimed invention at the time the application was filed. Nor has applicant described, with any degree of specificity, the claimed antibodies themselves.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed.

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state,

Art Unit: 1645

"[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by applicant in the specification; nor has applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has applicant described distinguishing identifying characteristics sufficient to show that applicant were in possession of the claimed invention at the time the application was filed.

As evidenced by Greenspan et al. (Nature Biotechnology 17: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows the epitope to which any given antibody binds can only be identified empirically. Even using a competition assay, the skilled artisan cannot determine whether an antibody binds the same epitope as another antibody because an antibody that competes with another does not necessarily bind the same epitope as the other; rather, one antibody may bind a spatially overlapping epitope to sterically hinder binding of the other. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of epitopes to which the members of the claimed genus of antibodies must bind, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of antibodies and one skilled in the art would not

Art Unit: 1645

recognize that applicant had possession of the claimed invention at the time the application was filed.

The rejection of claims 24 and 28 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is maintained for the reasons set forth in the previous office action.

The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation.

Applicant argues:

1. That the examiner's arguments that the specification does not describe the epitopes to which the claimed antibodies must bind are not relevant since there are no "claimed antibodies," as the claims are drawn to methods of "using antibodies that have been prepared against particular antigens."

2. That one of skill in the art could prepare and use such antibodies without further information or experimentation.

3. That the skilled artisan would know which type of sample to test for which type of infection, as evidenced by the examiner's statement that, for example, urine samples would not be predictive of dermatophytic infections.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, it is apparent, even based on applicant's arguments, that the claims recite antibodies, and it should be clear that these are the "claimed antibodies." It is also clear that methods of using antibodies require one to actually have the antibodies and that the specification must allow one to make and use these antibodies in order to make and use the method.

Regarding argument 2, despite applicant's assertion to the contrary, those of skill in the art would not be able to prepare the required antibodies and practice the claimed method for the reasons already set forth in the enablement rejection. Applicant's arguments have not addressed many of these issues. Foremost is the fact that, while those of skill in the art are quite capable of preparing antibodies that would allow detection of β -glucans, there is no means provided, in

Art Unit: 1645

either the art or the specification, that would allow one of skill in the art to prepare antibodies to *Candida* $\beta(1-3)$ - and/or a $\beta(1-3)$ (1-6)-glucan epitope in free form, or available in cell wall fragments of *C. albicans* and/or *C. neoformans*, or on the cell surface of *C. albicans*, *C. parapsilosis*, *C. krusei*, *C. glabrata* and/or *C. neoformans* that would allow one to diagnose *Candida* vaginitis or mucocutane candidiasis. In addition, even if one could differentiate *Candida* glucans from other species, the claimed method provides no way of determining whether the glucans are from the normal flora found in humans or from *Candida* causing *Candida* vaginitis or mucocutane candidiasis.

Regarding argument 3, the claims have been amended so that dermatophytic infections are no longer an issue. However, since $\beta(1-3)$ - and/or a $\beta(1-3)$ (1-6)-glucans from plants or other fungal species (particularly *Aspergillus* and *Cryptococcus*, which are human pathogens) could be found in mucosal secretions or urine, the method would still not allow diagnosis of *Candida* vaginitis or mucocutane candidiasis. Moreover, *Candida* species can be isolated from healthy mucosal surfaces of the oral cavity, vagina, gastrointestinal tract, and rectal area in as many as 80% of people in the absence of disease. The claimed method does not provide a way to differentiate between diseased persons and healthy persons.

As outlined previously, undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the claimed invention without undue experimentation.

Nature of the invention: The instant claims are drawn to methods for the diagnosis of a fungal infection (*Candida* vaginitis or mucocutane candidiasis) comprising assaying with at least one antibody that is reactive with a *Candida* $\beta(1-3)$ -glucan and/or a $\beta(1-3)$ (1-6)-glucan epitope in free form or available in cell wall fragments of *C. albicans* and/or *C. neoformans*, or on the cell surface of *C. albicans*, *C. parapsilosis*, *C. krusei*, *C. glabrata* and/or *C. neoformans*.

Breadth of the claims: The instant claims are drawn to all antibodies with specificity to any $\beta(1,3)$ - and/or $\beta(1,3)(1,6)$ -glucan epitope (claims 24-25). Claim 28 is drawn to all monoclonal antibodies with specificity to any $\beta(1,3)$ - and/or $\beta(1,3)(1,6)$ -glucan epitope. With

Art Unit: 1645

the exception of claim 25, the claims are drawn to methods of diagnosing all fungal infections of all types. This would include every species of fungus capable of causing infection, and it would include mycoses of all types, including systemic, epidermal, nail, and gastrointestinal infections. The claims encompass antibodies directed to $\beta(1-3)$ - and/or a $\beta(1-3)$ (1-6)-glucan epitopes from all organisms.

Working Examples/Guidance of Specification: The specification fails to describe immunoepitopes against which the claimed antibodies are raised and must subsequently bind. The working examples disclose specific antibodies that meet the limitations of the instant claims. However, these "examples" refer to antibodies by their laboratory designations which are not sufficient to provide enablement for the full scope of the rejected claims. The specification is silent as to what specific "immunoepitope" meets the limitations of the claims. Additionally, the specification is silent with regard to what epitopes are cross-reactive and what epitopes would allow one to differentiate between species. There is no showing in the specification that either A10A, or any other antibodies can be used to detect infection using any type of sample. The only information regarding A10A or other antibodies is that they are capable of binding $\beta(1-3)$ - and/or a $\beta(1-3)$ (1-6)-glucans. The specification states that $\beta(1,3)$ -glucan has been found in the serum of all patients with candidemia, but in none of women with superficial Candida infection, or in healthy controls (page 14). The specification further states that "the presence of $\beta(1,3)$ -glucans in the serum of patients with deep fungal infections may be a useful marker for laboratory diagnosis of these infections. Future investigations will address the usefulness of our mAbs to glucan in an immunoassay-based kit for the rapid detection of $\beta(1,3)$ -glucans in blood samples, in other specimens from patients with invasive fungal infections, or in other body fluids such as mucosal secretions and urine." All guidance regarding the claimed method is prophetic.

State of the prior art and Unpredictability of the art: In the instant application, applicant has failed to "fully characterize" the antigen (i.e. $\beta(1,3)$ - and/or $\beta(1,3)(1,6)$ -glucan associated epitopes) to which the claimed antibody binds. The instant claims are drawn to methods utilizing all antibodies with specificity to any $\beta(1,3)$ - and/or $\beta(1,3)(1,6)$ -glucan associated epitopes. Consequently, since applicant has not fully characterized the antigen to which the claimed antibodies bind, hence the skilled artisan would not be able to make the claimed invention.

While the skill in the art of immunology is high, to date, prediction of a specific immune response for any given composition in any given animal is quite unpredictable. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally, Greenspan et al. (Nature Biotechnology 17: 936-937, 1999), disclose defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a particular immune response (i.e. generation of an antibody that bind to a given epitope) can only be identified empirically. This constitutes undue experimentation. Therefore, given the lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the generation of a specific immune response, the specification does not enable any person of skill in the art to which it pertains, or with which it is most nearly connected, to make and use the claimed invention.

With regard to methods of diagnosing fungal infections, monoclonal antibodies capable of binding to $\beta(1,3)$ -glucans have been shown in the art, and assays exist for determining the presence of $\beta(1,3)$ -glucans in environmental samples, as well as serum samples. Tamura et al. (J. Clin. Lab. Anal., 11:104-109, 1997) disclose an assay to detect *Candida* $\beta(1,3)$ -glucans in murine serum samples (see Results). Milton et al. (Appl. Environ. Microbiol., 67:5420-5424, 2001) present an ELISA to determine the presence of $\beta(1,3)$ -glucans in environmental samples (see whole article). However, these studies have shown an ability to detect $\beta(1,3)$ -glucans, not to diagnose infection, or to determine the presence of fungal cells, especially in specific areas of the body. Tamura only studied serum samples, and in these did not show a statistically valid correlation between fungal cells and $\beta(1,3)$ -glucans. Using methods other than antibody detection, Odabasi et al. (Clin. Infect. Dis., 39:199-205, 2004) found serum samples that were positive for $\beta(1,3)$ -glucans in patients with no known fungal infections, and found serum samples that were negative for $\beta(1,3)$ -glucans in patients that likely had fungal infections (see page 204, column 1, paragraph 3 – column 2, paragraph 2; see also, table 2). Murray et al. (Medical Microbiology, 4th ed., 2002) state that *Candida* species can be isolated from healthy mucosal surfaces of the oral cavity, vagina, gastrointestinal tract, and rectal area. As many as 80% of people may show colonization of these sites in the absence of disease (see page 664, column 2, paragraph 3).

Therefore, while monoclonal antibodies may be used to detect the presence and the amount of $\beta(1,3)$ -glucans present in a sample, this is not correlated with infection. Applicants have not shown the method to be effective, and only prophetically discuss said method. Applicants stated that in patients with superficial infection, no $\beta(1,3)$ -glucans were found in serum. This is in agreement with the art that shows that $\beta(1,3)$ -glucans were not detected in some infected patients. The skilled artisan would expect that urine samples would not be predictive of dermatophytic infections, and that oral samples would not be predictive of vaginal infections. Further, one would be unable to distinguish between *Candida* vaginitis or mucocutane candidiasis and the normal colonization that is found in 80% of the population using said method. Moreover, the epitopes to which the claimed antibodies must bind are present in many species. One would be unable to distinguish between these species using the claimed

Art Unit: 1645

methods, and since said epitopes can be found on plant cells, one could not even determine if the $\beta(1,3)$ -glucans were fungal in origin.

Therefore, in view of the lack of guidance in the specification and the art, the specification does not enable one of skill in the art to use the invention as claimed.

New Claim Rejections

35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 24 and 28 are rendered vague and indefinite by the phrase “wherein the fungal infection is *Candida vaginitis* or mucocutane candidiasis.”

This is essentially the rejection previously set forth for claim 25. Claim 25 has been cancelled and this limitation was added to claims 24-28. Applicant has argued that the claims have been amended, and asked that, if the language is still unclear, the examiner suggest language that would overcome this rejection.

Since the claims have been amended to recite the same phrase that was originally rejected, the language is still unclear. *Candida vaginitis* is a disease caused by a fungal infection, it is not the infection itself. In addition, mucocutane candidiasis is a heterogeneous disorder of the immune system that is characterized by persistent *Candida* infections of the mucous membranes. As with *Candida vaginitis*, mucocutane candidiasis is a disease caused by a fungal infection, and it is not the fungal infection itself. To overcome this rejection, it is suggested that the limitation be deleted or the claim could be amended to recite “method for the diagnosis of *Candida vaginitis* or mucocutane candidiasis.” It is noted that this suggested language would overcome only the instant rejection under 35 U.S.C. 112, second paragraph and does not address any other rejections that are pending or that may be raised by the amendment.

Art Unit: 1645

Claims 24 and 28 are rendered vague and indefinite by the phrase "a *Candida* $\beta(1-3)$ glucan - and/or a $\beta(1-3)(1-6)$ - glucan epitope." It is not clear if the modifier, *Candida* is meant to apply just to the term " $\beta(1-3)$ glucan" or whether it is meant to apply to the term " $\beta(1-3)$ glucan" and the term " $\beta(1-3)(1-6)$ - glucan."

Claims 24 and 28 are rendered vague and indefinite by their reference to the organism, "*C. neoformans*." First, in the system of binomial nomenclature used by scientists, an organism is referred to by its genus name and its species name. The first recitation of an organism's name should include the full recitation of the genus name, which can thereafter be abbreviated using the first letter. However, this can be done only when the meaning is completely unambiguous and no other genus name beginning with the same letter is used in intervening text. In the instant case, the claim refers to the genus *Candida* and refers to *C. neoformans*, which means that the claim is referring to *Candida neoformans*. There is no such organism to be found in the art. If applicant is referring to *Cryptococcus neoformans*, then no abbreviations of the genus should be used. Furthermore, it is not clear how an antibody to *Cryptococcus neoformans* could be used to diagnose a *Candida* infection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRIAN J. GANGLE whose telephone number is (571)272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1645

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brian J Gangle
Examiner, Art Unit 1645

/Shanon A. Foley/
Supervisory Patent Examiner, Art Unit 1645